IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Randolph J. Noelle et al.

Application No.: 09/849,969 Confirmation No.: 1327

Filed: May 8, 2001 Art Unit: 1644

For TREATMENT OF T CELL MEDIATED IMMUNE DISORDERS Examiner: P. Gambel

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Concurrent with the filing of a Notice of Appeal, and in accordance with the Pre-Appeal Brief Conference Program, Applicants hereby request a pre-Appeal Brief review of the final rejection mailed February 7, 2007 in this application. No amendments are being filed with this request. With all claims having been twice rejected, an appeal is proper in accordance with 37 C.F.R. § 41.31(a).

Claims 1, 5-10, 17 and 19 are pending in this application. The sole question on appeal is whether the Examiner is correct in rejecting the claims under 35 U.S.C. § 103 as obvious over Lederman *et al.*, U.S. Patent No. 6,592,868 ("Lederman"), in view of U.S. Patent No. 5,747,037 issued to Noelle ("Noelle").

In order to make a showing of obviousness, the Examiner must make the four factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17-18 (U.S. 1966): (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations, such as long felt need, commercial success, and unexpected results. *See KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1734, 167 L.Ed.2d 705,

715 (2007). Review is being requested because the differences between the prior art and the currently claimed invention are too great to render the claims obvious, and more importantly, the Examiner has not properly considered the evidence of unexpected results that is of record in this application.

The present claims call for method for preventing *T cell mediated* tissue destruction associated with type 1 diabetes comprising the administration of a gp39 antagonist, wherein the tissue destruction results from a *T cell mediated immune reaction* to an autoantigen.

Lederman is limited to inhibiting B cell activation in autoimmune diseases and discusses diabetes exclusively in the *context of B cell activation, not in the context of preventing a T cell mediated autoimmune disorder* (Lederman, col. 11, ll. 18-35). *See* Response dated November 6, 2006, pages 9-10; Response dated April 9, 2007, page 6. While it was known in the art in June of 1995 that the immune response in type I diabetes had both B cell- and T cell-mediated components, nothing in the teachings or disclosure of Lederman suggests that the disclosed method can be used to treat the T cell-mediated aspects of diabetes. *See* Declaration of Clark, ¶¶ 13, 18 and 19; Response dated November 6, 2006, page 13; Response dated April 9, 2007, page 6. Dr Clark, a renowned expert in the field, reported that because these are two completely separate immune responses, in June of 1995, the suggestion to use a method to treat one would not have led a person of skill in the art to even try the same method to treat the other. *See* Declaration of Clark, ¶ 9; Response dated November 6, 2006, page 12; Response dated April 9, 2007, page 6. Thus, the disclosure of Lederman does not teach or suggest the presently claimed invention.

Additionally, Lederman does not even teach a person of skill in the art to treat B cell-mediated diseases because there are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. There are no data showing the effect of normal human T cells expressing what is called T-BAM on an immune response *in vitro* or *in vivo*. There are no functional data in Lederman using T cells activated with physiologic stimuli, *i.e.*, antigen, and no data assessing the role of an anti-CD40L antibody *in vivo* which would be essential to know if the antibody could inhibit autoimmune disease. *See* Declaration of Clark, ¶¶ 20-24; Response dated November 6, 2006, page 15-16; Response dated April 9, 2007, page 7.

The Noelle '037 patent discloses a method for inducing antigen-specific T cell tolerance and a means to block allogeneic T cell responses as measured by graft versus host disease (GVHD) using anti-gp39 monoclonal antibodies. One skilled in the art at the time the present invention was made might have thought that this treatment may be pertinent for the treatment of diabetes to the extent that the method in Noelle involves pancreatic allografts (Declaration of Clark, ¶ 17; Response dated November 6, 2006, page 16; Response dated April 9, 2007, page 8). However, this would not suggest that the underlying diabetes could be directly treated with an anti-gp39 antagonist. Nor was it known or suggested in June of 1995 that pancreatic allograft rejection could be treated with anti-CD40L antagonists. In short, the Noelle '037 patent concerns the induction of antigen-specific T cell tolerance that would be applicable to allogeneic transplantation or autoimmune disease where the autoantigens are clearly defined. *Id.*

Thus, when the teachings of the prior art, Lederman and Noelle, are compared to the presently claimed method, in view of the state of the art in June of 1995, it can be seen that the differences between them are far too great to render the present claims obvious.

Additionally, the claimed method of treating T cell-mediated tissue destruction is unexpected given the state of the art and the teachings of the cited prior art references. As discussed fully in the Responses filed November 6, 2006 and April 9, 2007, and the Declaration of Edward Clark, there are two distinct and different types of immune responses, B cell-mediated, or humoral, and T cell-mediated or cellular (Clark Declaration, ¶¶ 3-8, Response dated November 6, 2006, pages 10-12; Response dated April 9, 2007, pages 8-9). While it was known in June of 1995 that type I diabetes involved both B cell-mediated and T cell-mediated responses, it was not known at the time that gp39 had a role in immune responses other than humoral, *i.e.*, those involving T cell-B cell interactions. *See* Clark Declaration, ¶¶ 9-13, Exhibits D, E, F, and H to Clark Declaration; Response dated November 6, 2006, page 12; Response dated April 9, 2007, page 10. The first study to even suggest the role of CD40-CD40L in T cell-mediated immune responses was published in November of 1997, almost a year and a half after the invention date. *See* Declaration of Clark, ¶ 15, Exhibit K to Clark Declaration. Thus, at the time of the present invention, one of ordinary skill in the antibody art would not have recognized that a gp39 antagonist would have an effect on T cell-mediated disease because the response to the autoantigen is independent of B cell activation, which was considered the primary role of

gp39. Nor would he have expected success in treating T cell-mediated responses in type I diabetes with an anti-gp39 antibody from these early teachings.

The Examiner states that the Applicants are relying upon mechanisms of action of the asserted teachings of the prior art and has not distinguished the expectation of success in treating a patient with diabetes with a gp39/CD40L/5c8 antagonist based upon the teachings of the prior art. *See* Final Office Action dated February 6, 2007, page 7. Applicants respectfully submit it is more than a difference in mechanism of action that distinguishes the present invention over the teachings of the prior art. The treatment of "tissue damage [that] results from a T cell mediated immune reaction to an autoantigen" by a patient with type I diabetes that is called for in the present claims is different than treating tissue damage resulting from B cell mediated immune reactions. The former involves treating inflammation and destruction of beta cells by macrophages and cytotoxic T cells, while the latter involves autoantibodies. As explained by Dr Clark, tissue damage caused by a T cell mediated immune reaction to an autoantigen was not considered treatable by gp39 antagonists in June of 1995. *See* Declaration of Clark, ¶¶ 14, 16; Response dated November 6, 2006, pages 10-12; Response dated April 9, 2007, pages 9-10.

It is also respectfully submitted that the evidence submitted with the April 1, 2005 reply (Noelle Declaration (Exhibit D) and Exhibits B and C) as to the unexpected superior results of the 24-31 antibody *in vivo* as compared to the 5c8 antibody has not been accorded its due weight. In addition to being therapeutically safe by not causing thomboses (contrary to hu5c8), the antibodies called for in the present claims block binding of CD40 to gp39 *in vivo* more effectively than 5c8. This powerful objective evidence of superior results weighs heavily in favor of patentability but has been accorded little or no consideration. *See* Response dated November 6, 2006, page 17; Response dated April 9, 2007, pages 10-11.

Therefore, claim 1 is believed to be patentable over the cited art. In view of the patentability of this claim, claims 5-10, 17 and 19, which depend from this independent claim, are also believed to be patentable. Applicants respectfully request reconsideration and withdrawal of this rejection. For the reasons demonstrated above, the case should be returned to the Examiner with an indication that the application is allowable.

Dated: October 17, 2007

Respectfully submitted,

By _____

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